(including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Specification:

Please substitute the following paragraphs for the pending paragraphs.

Please substitute the paragraph beginning on page 4, line 22, with the following paragraph:

C1

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a TR2 receptor and splice variants thereof having the amino acid sequences shown in FIG. 1A-1B (SEQ ID NO:2), FIG. 4A-4C (SEQ ID NO:5) and FIG. 7A-7C (SEQ ID NO:8) or the amino acid sequence encoded by the cDNA clone encoding the TR2 receptors deposited in bacterial hosts as ATCC Deposit Numbers 97059, 97058 and 97057 on February 13, 1995. The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them for production of TR2 polypeptides or peptides by recombinant techniques.

Please substitute the paragraph beginning on page 6, line 22, with the following paragraph:

C2

FIG. 2 shows the regions of similarity between the amino acid sequences of the TR2 receptor protein of FIG. 1A-1B and a murine CD40 protein (SEQ ID NO:3) (percent similarity: 46.591; percent identity: 28.788).

Please substitute the paragraph beginning on page 7, line 4, with the following paragraph:

C3

FIG. 4A-4C shows the nucleotide (SEQ ID NO:4) and deduced amino acid (SEQ ID NO:5) sequences of the TR2-SV1 receptor. The protein has a predicted leader sequence of about 36 amino acid residues (underlined) (amino acid residues -36 to -1 in SEQ ID NO:5) and a deduced molecular weight of about 19.5 kDa.

Please substitute the paragraph beginning on page 7, line 9, with the following paragraph:

C4

FIG. 5 shows the regions of similarity between the amino acid sequences of the full-length TR2-SV1 receptor protein and a human type 2 TNF receptor (SEQ ID NO:6) (percent similarity is 47.541; percent identity: 24.590).

Please substitute the paragraph beginning on page 7, line 12, with the following paragraph:

C5

FIG. 6 shows an analysis of the TR2-SV1 receptor amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues 39 to 70, 99 to 136 and 171 to 185 in FIG. 4A-4C (amino acid residues 3 to 34, 63 to 100 and 135 to 149 in SEQ ID NO:5) correspond to the shown highly antigenic regions of the TR2-SV1 receptor protein.

Please substitute the paragraph beginning on page 7, line 19, with the following paragraph:

C6

FIG. 7A-7C shows the nucleotide (SEQ ID NO:7) and deduced amino acid (SEQ ID NO:8) sequences of the TR2-SV2 receptor. This protein lacks a putative leader sequence and has a deduced molecular weight of about 14 kDa.

Please substitute the paragraph beginning on page 7, line 22, with the following paragraph:

C7 FIG. 8 shows the regions of similarity between the amino acid sequences of the TR2-SV2 receptor protein and a human type 2 TNF receptor (SEQ ID NO:9) (percent similarity: 45.522; percent identity: 26.866).

Please substitute the paragraph beginning on page 7, line 25, with the following paragraph:

C8 FIG. 9 shows an analysis of the TR2-SV2 receptor amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues 56 to 68 and 93 to 136 in FIG. 7A-7C (SEQ ID NO:8) correspond to the shown highly antigenic regions of the TR2-SV2 receptor protein.

Please substitute the paragraph beginning on page 8, line 3, with the following paragraph:

C9 FIG. 10 shows the regions of similarity between the amino acid sequences of the TR2 receptor protein of FIG. 1A-1B and the TR2-SV1 receptor protein of FIG. 4A-4C (percent similarity: 73.370; percent identity: 9.783).

Please substitute the paragraph beginning on page 8, line 6, with the following paragraph:

C10 FIG. 11 shows the regions of similarity between the amino acid sequences of the TR2 receptor protein of FIG. 1A-1B and the TR2-SV2 receptor protein of FIG. 7A-7C (percent similarity: 70.588; percent identity is 60.294).

Please substitute the paragraph beginning on page 8, line 9, with the following paragraph:

C 11

FIG. 12 shows the regions of similarity between the amino acid sequences of the TR2-SV1 and the TR2-SV2 receptor proteins (percent similarity: 37.984; percent identity: 20.155).

Please substitute the paragraph beginning on page 8, line 11, with the following paragraph:

C 12

FIG. 13A-13D shows the regions of similarity between the nucleotide sequences encoding the TR2 receptor protein of FIG. 1A-1B and the TR2-SV1 receptor protein of FIG. 4A-4C (percent similarity: 92.168; percent identity: 92.168).

Please substitute the paragraph beginning on page 8, line 14, with the following paragraph:

C 13

FIG. 14A-14D shows the regions of similarity between the nucleotide sequences encoding the TR2 receptor protein of FIG. 1A-1B and the TR2-SV2 receptor protein of FIG. 7A-7C.

Please substitute the paragraph beginning on page 8, line 17, with the following paragraph:

C 14

FIG. 15A-15F shows the regions of similarity between the nucleotide sequences encoding the TR2-SV1 and the TR2-SV2 receptor proteins (percent similarity: 53.479; percent identity: 53.479).

Please substitute the paragraph beginning on page 8, line 25, with the following paragraph:

C 15

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a TR2 polypeptide (FIG. 1A-1B (SEQ ID NO:2)) and splice variants thereof, TR2-SV1 (FIG. 4A-4C (SEQ ID NO:5)) and TR2-SV2 (FIG. 7A-7C (SEQ ID NO:8)), the amino acid sequences of which were determined by sequencing cloned cDNAs. The TR2 protein shown in

FIG. 1A-1B shares sequence homology with the murine CD40 receptor (FIG. 2 (SEQ ID NO:3)). On February 13, 1995 a deposit was made at the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, and given accession number 97059. The nucleotide sequence shown in FIG. 1A-1B (SEQ ID NO:1) was obtained by sequencing a cDNA clone (Clone ID HLHAB49) containing the same amino acid coding sequences as the clone in ATCC Accession No. 97059 with minor deviation. The cDNA sequence shown in FIG. 1A-1B (SEQ ID NO:1) differs from that of the ATCC deposit in the 5' and 3' noncoding nucleotide sequences and three nucleotides.

C 15 cont.

Please substitute the paragraph beginning on page 10, line 1, with the following paragraph:

C 16

The nucleotide sequences shown in FIG. 4A-4C (SEQ ID NO:4) and FIG. 7A-7C (SEQ ID NO:7) were also obtained by sequencing cDNA clones deposited on February 13, 1995 at the American Type Culture Collection and given accession numbers 97058 (TR2-SV1) and 97057 (TR2-SV2), respectively. The deposited clones are contained in the pBluescript SK(-) plasmid (Stratagene, LaJolla, CA).

Please substitute the paragraph beginning on page 10, line 14, with the following paragraph:

C 17

As used herein, "TR2 proteins", "TR2 receptors", "TR2 receptor proteins" and "TR2 polypeptides" refer to all proteins resulting from the alternate splicing of the genomic DNA sequences encoding proteins having regions of amino acid sequence identity and receptor activity which correspond to the proteins shown in FIG. 1A-1B (SEQ ID NO:2), FIG. 4A-4C (SEQ ID NO:5) or FIG. 7A-7C (SEQ ID NO:8). The TR2 protein shown in FIG. 1A-1B, the TR2-SV1

C17 cont.

protein shown FIG. 4A-4C and the TR2-SV2 protein shown in FIG. 7A-7C are examples of such receptor proteins.

Please substitute the paragraph beginning on page 11, line 13, with the following paragraph:

C18

Using the information provided herein, such as the nucleotide sequence in FIG. 1A-1B, FIG. 4A-4C or FIG. 7A-7C, nucleic acid molecules of the present invention encoding TR2 polypeptides may be obtained using standard cloning and screening procedures, such as those used for cloning cDNAs using mRNA as starting material. Illustrative of the invention, the nucleic acid molecule described in FIG. 1A-1B (SEQ ID NO:1) was discovered in a cDNA library derived from activated human T-lymphocytes. The nucleic acid molecules described in FIG. 4A-4C (SEQ ID NO:4) and FIG. 7A-7C (SEQ ID NO:7) were discovered in cDNAs library derived from human fetal heart and human stimulated monocytes, respectively.

Please substitute the paragraph beginning on page 12, line 15, with the following paragraph:

C19

Similarly, the determined cDNA nucleotide sequences of the TR2-SV1 splice variant of TR2 (FIG. 4A-4C (SEQ ID NO:4)) contains an open reading frame encoding a protein of about 185 amino acid residues, with a predicted leader sequence of about 36 amino acid residues, and a deduced molecular weight of about 19.5 kDa. The amino acid sequence of the predicted mature TR2-SV1 receptor is shown in FIG. 4A-4C (SEQ ID NO:5) from amino acid residue about 37 to residue about 185 (amino acid residues 1 to 149 in (SEQ ID NO:5). The TR2-SV1 protein shown in FIG. 4A-4C (SEQ ID NO:5) is about 25% identical and about 48% similar to the human type 2 TNF receptor protein shown in SEQ ID NO:6 (see FIG. 5).

Please substitute the paragraph beginning on page 12, line 25, with the following paragraph:

C 20

The determined cDNA nucleotide sequences of the TR2-SV2 splice variant of TR2 (FIG. 7A-7C (SEQ ID NO:7)) contains an open reading frame encoding a protein of about 136 amino acid residues, without a predicted leader sequence, and a deduced molecular weight of about 14 kDa. The amino acid sequence of the predicted TR2-SV2 receptor is shown in FIG. 7A-7C (SEQ ID NO:8) from amino acid residue about 1 to residue about 136. The TR2-SV2 protein shown in FIG. 7A-7C (SEQ ID NO:8) is about 27% identical and about 45% similar to the human type 2 TNF receptor protein shown in SEQ ID NO: 9 (see FIG. 8).

Please substitute the paragraph beginning on page 13, line 5, with the following paragraph:

C 21

A comparison of both the nucleotide and amino acid sequences of the TR2, TR2-SV1 and TR2-SV2 receptor proteins shown in FIG. 1A-1B, FIG. 4A-4C and FIG. 7A-7C shows several regions of near identity. While the amino acid sequence of the TR2 receptor protein, shown in FIG. 1A-1B (SEQ ID NO:2), is about 60% identical and about 73% similar to the amino acid sequence of the TR2-SV1 receptor protein, shown in FIG. 4A-4C (SEQ ID NO:5), in approximately the first one hundred amino acids of their respective sequences the two proteins differ in one location (FIG. 10).

Please substitute the paragraph beginning on page 13, line 13, with the following paragraph:

C 22

Similarly, the amino acid sequence of the TR2 receptor protein of FIG. 1A-1B (SEQ ID NO:2) is about 60% identical and about 71% similar to the amino acid sequence of the TR2-SV2 receptor protein, shown in FIG. 7A-7C (SEQ ID NO:8); however, the two proteins are almost identical over a 60 amino acid stretch in the central portion of the TR2-SV2 protein (FIG. 11).

Please substitute the paragraph beginning on page 13, line 23, with the following paragraph:

With respect to their nucleotide sequences of the cDNAs encoding the disclosed TR2 proteins, a comparison of these sequences indicates that the TR2 cDNAs share large regions of near identity at the nucleic acid level (FIG. 13A-13D, FIG. 14A-14D and FIG. 15A-15F). The cDNA sequences encoding the TR2 and TR2-SV1 proteins, for example, share large regions of near identity in their nucleotide sequences which encode both the N termini of the respective proteins and their 5' and 3' noncoding regions (FIG. 13A-13D). Further, the nucleotide sequences of the cDNAs encoding the TR2-SV1 and TR2-SV2 proteins share considerable homology but this identity is limited to their 3' regions well beyond their respective coding sequences (FIG. 15A-15F).

C23

Please substitute the paragraph beginning on page 14, line 25, with the following paragraph:

In the present instance, the TR2 receptor protein shown in FIG. 1A-1B (SEQ ID NO:2) is believed to be the full-length polypeptide encoded by the RNA from which the TR2 receptor proteins are translated. The RNA encoding the TR2-SV1 splice variant shown in FIG. 4A-4C (SEQ ID NO:5) is believed to contain an insertion in the region encoding amino acid residue 102 of the amino acid sequence shown in FIG. 1A-1B and a deletion in the region encoding amino acid residue 184 of the amino acid sequence shown in FIG. 1A-1B. The RNA encoding the TR2-SV2 splice variant shown in FIG. 7A-7C is believed to begin with the nucleotide sequence encoding amino acid residue 102 of the amino acid sequence shown in FIG. 1A-1B and contain insertions in the regions encoding amino acid residues 184 and 243 of the amino acid sequence shown in FIG. 1A-1B.

C24

Please substitute the paragraph beginning on page 15, line 8, with the following paragraph:

As indicated, the present invention also provides the mature forms of the TR2 receptors of the present invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species on the protein. Further, it has long been known that the cleavage specificity of a C25 secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide. Therefore, the present invention provides nucleotide sequences encoding mature TR2 polypeptides having the amino acid sequences encoded by the cDNA clones contained in the host identified as ATCC Deposit Numbers 97059 and 97058 and as shown in FIG. 1A-1B (SEQ ID NO:2) and FIG. 4A-4C (SEQ ID NO:5). By the mature TR2 polypeptides having the amino acid sequences encoded by the cDNA clones contained in the host identified as ATCC Deposit Numbers 97059 and 97058 is meant the mature form(s) of the TR2 receptors produced by expression in a mammalian cell (e.g., COS cells, as described below) of the complete open reading frame encoded by the human DNA sequence of the clone contained in the vector in the deposited host.

Please substitute the paragraph beginning on page 15, line 28, with the following paragraph:

The invention also provides nucleic acid sequences encoding the TR2-SV2 receptor protein C26 of FIG. 7A-7C (SEQ ID NO:8), having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 97057, which does not contain a secretory leader sequence.

Please substitute the paragraph beginning on page 16, line 10, with the following paragraph:

In the present case, the predicted amino acid sequences of the complete TR2 polypeptides shown in FIG. 1A-1B (SEQ ID NO:2), FIG. 4A-4C (SEQ ID NO:5) and FIG. 7A-7C (SEQ ID NO:8) were analyzed by a computer program ("PSORT") (K. Nakai and M. Kanehisa, *Genomics 14*:897-911 (1992)), which is an expert system for predicting the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis by the PSORT program predicted the cleavage sites between amino acids -1 and 1 in SEQ ID NO:2 and SEQ ID NO:5. Thereafter, the complete amino acid sequences were further analyzed by visual inspection, applying a simple form of the (-1,-3) rule of von Heine. von Heinje, *supra*. Thus, the leader sequences for the TR2 protein shown in SEQ ID NO:2 and the TR2-SV1 protein are predicted to consist of amino acid residues -36 to -1 in both SEQ ID NO:2 and SEQ ID NO:5, while the predicted mature TR2 proteins consist of amino acid residues 1 to 247 for the TR2 protein shown in SEQ ID NO:2 and residues 1 to 149 for the TR2-SV1 protein shown in SEQ ID NO:5.

C27

Please substitute the paragraph beginning on page 18, line 12, with the following paragraph:

Similarly, isolated nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) shown in FIG. 4A-4C (SEQ ID NO:4); DNA molecules comprising the coding sequence for the mature TR2-SV1 receptor shown in FIG. 4A-4C (SEQ ID NO:5) (last 149 amino acids); and DNA molecules which comprise a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode the TR2-SV1 receptor.

C28

Please substitute the paragraph beginning on page 18, line 19, with the following paragraph:

C29 Further, isolated nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) shown in FIG. 7A-7C (SEQ ID NO:7) and DNA molecules which comprise a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode the TR2-SV2 receptor.

Please substitute the paragraph beginning on page 18, line 24, with the following paragraph:

C30 In another aspect, the invention provides isolated nucleic acid molecules encoding the TR2, TR2-SV1 and TR2-SV2 polypeptides having the amino acid sequences encoded by the cDNA clones contained in the plasmid deposited as ATCC Deposit No. 97059, 97058 and 97057, respectively, on February 13, 1995. In a further embodiment, these nucleic acid molecules will encode a mature polypeptide or the full-length polypeptide lacking the N-terminal methionine. The invention further provides isolated nucleic acid molecules having the nucleotide sequences shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), and FIG. 7A-7C (SEQ ID NO:7); the nucleotide sequences of the cDNAs contained in the above-described deposited clones; or nucleic acid molecules having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful as probes for gene mapping, by *in situ* hybridization with chromosomes, and for detecting expression of the TR2 receptor genes of the present invention in human tissue, for instance, by Northern blot analysis.

Please substitute the paragraph beginning on page 19, line 10, with the following paragraph:

C31 The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated nucleic acid molecule having the nucleotide

sequence of the deposited cDNAs or the nucleotide sequence shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), or FIG. 7A-7C (SEQ ID NO:7) is intended fragments at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-400 nt in length are also useful according to the present invention as are fragments corresponding to most, if not all, of the nucleotide sequences of the deposited cDNAs or as shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), or FIG. 7A-7C (SEQ ID NO:7). By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequences of the deposited cDNAs or the nucleotide sequences as shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), or FIG. 7A-7C (SEQ ID NO:7).

C 31 cont.

Please substitute the paragraph beginning on page 20, line 9, with the following paragraph:

Preferred nucleic acid fragments of the present invention also include nucleic acid molecules encoding polypeptides comprising the mature TR2-SV1 receptor (predicted to constitute amino acid residues from about 37 to about 185 in FIG. 4A-4C (amino acid residues 1 to 149 in SEQ ID NO:5)) and the complete TR2-SV2 receptor (predicted to constitute amino acid residues from about 1 to about 136 in FIG. 7A-7C (SEQ ID NO:8)).

C 32

Please substitute the paragraph beginning on page 20, line 20, with the following paragraph:

Preferred nucleic acid fragments of the present invention also include nucleic acid molecules encoding epitope-bearing portions of the TR2 receptor proteins. In particular, such nucleic acid fragments of the present invention include nucleic acid molecules encoding: a

C 33

polypeptide comprising amino acid residues from about 39 to about 70 in FIG. 1A-1B (amino acid residues 3 to 34 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 106 to about 120 in FIG. 1 (amino acid residues 70 to 84 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 142 to about 189 in FIG. 1A-1B (amino acid residues 106 to 153 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 276 to about 283 in FIG. 1A-1B (amino acid residues 240 to 247 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 39 to about 70 in FIG. 4A-4C (amino acid residues 3 to 34 in SEQ ID NO:5); amino acid residues from about 99 to about 136 in FIG. 4A-4C (amino acid residues 63 to 100 in SEQ ID NO:5); amino acid residues from about 171 to about 185 in FIG. 4A-4C (amino acid residues 135 to 149 in SEQ ID NO:5); amino acid residues from about 56 to about 68 in FIG. 7A-7C (SEQ ID NO:8); amino acid residues from about 93 to about 136 in FIG. 7A-7C (SEQ ID NO:8). The inventors have determined that the above polypeptide fragments are antigenic regions of the TR2 receptors. Methods for determining other such epitope-bearing portions of the TR2 proteins are described in detail below.

C 33 cont.

Please substitute the paragraph beginning on page 21, line 28, with the following paragraph:

By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., the deposited cDNAs or the nucleotide sequences as shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), or FIG. 7A-7C (SEQ ID NO:7)).

C 34

Please substitute the paragraph beginning on page 22, line 4, with the following paragraph:

Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3' terminal poly(A) tract of the TR2 receptor cDNA sequences shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), or FIG. 7A-7C (SEQ ID NO:7)), or to a complementary stretch of T (or U) resides, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

C35

Please substitute the paragraph beginning on page 23, line 22, with the following paragraph:

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to (a) a nucleotide sequence encoding the TR2 polypeptide having the complete amino acid sequence shown in FIG. 1A-1B (amino acid residues -36 to 247 in SEQ ID NO:2), FIG. 4A-4C (amino acid residues -36 to 149 in SEQ ID NO:5), or FIG. 7A-7C (amino acid residues 1 to 136 in SEQ ID NO:8); (b) a nucleotide encoding the complete amino sequence shown in FIG. 1A-1B (amino acid residues -35 to 247 in SEQ ID NO:2), FIG. 4A-4C (amino acid residues -35 to 149 in SEQ ID NO:5), or FIG. 7A-7C (amino acid residues 2 to 136 in SEQ ID NO:8) but lacking the N-terminal methionine; (c) a nucleotide sequence encoding the mature TR2 receptors (full-length polypeptide with any attending leader sequence removed) having the amino acid sequence at positions from about 37 to about 283 in FIG. 1A-1B (amino acid residues 1 to 247 in SEQ ID NO:2) or the amino acid sequence at positions from about 37 to about 185 in FIG. 4A-4C (amino acid residues 1 to 149 in SEQ ID NO:5), or the amino acid sequence at

C36

positions from about 1 to about 136 in FIG. 7A-7C (SEQ ID NO:8); (d) a nucleotide sequence encoding the TR2, TR2-SV1 or TR2-SV2 polypeptides having the complete amino acid sequence including the leader encoded by the cDNA clones contained in ATCC Deposit Numbers 97059, 97058, and 97057, respectively; (e) a nucleotide sequence encoding the mature TR2 or TR2-SV1 receptors having the amino acid sequences encoded by the cDNA clones contained in ATCC Deposit Numbers 97059 and 97058, respectively; (f) a nucleotide sequence encoding the TR2 or TR2-SV1 receptor extracellular domain; (g) a nucleotide sequence encoding the TR2 receptor transmembrane domain; (h) a nucleotide sequence encoding the TR2 receptor intracellular domain; (i) a nucleotide sequence encoding the TR2 receptor extracellular and intracellular domains with all or part of the transmembrane domain deleted; and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i).

C36 cont.

Please substitute the paragraph beginning on page 25, line 24, with the following paragraph:

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), or FIG. 7A-7C (SEQ ID NO:7) or to the nucleic acid sequence of the deposited cDNAs, irrespective of whether they encode a polypeptide having TR2 receptor activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having TR2 receptor activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having TR2 receptor activity include, *inter alia,* (1) isolating a TR2 receptor gene or allelic or splice variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal

C37

C37 Cont.

spreads to provide precise chromosomal location of a TR2 receptor gene, as described in Verma *et al., Human Chromosomes: A Manual of Basic Techniques*, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting TR2 receptor mRNA expression in specific tissues.

Please substitute the paragraph beginning on page 26, line 11, with the following paragraph:

C38

Preferred, however, are nucleic acid molecules having sequences at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4), or FIG. 7A-7C (SEQ ID NO:7) or to the nucleic acid sequence of the deposited cDNAs which do, in fact, encode a polypeptide having TR2 receptor activity. By "a polypeptide having TR2 receptor activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of the TR2 receptors of the present invention (either the full-length protein, the splice variants, or, preferably, the mature protein), as measured in a particular biological assay. For example, TR2 receptor activity can be measured by determining the ability of a polypeptide-Fc fusion protein to inhibit lymphocyte proliferation as described below in Example 6. TR2 receptor activity may also be measured by determining the ability of a polypeptide, such as cognate ligand which is free or expressed on a cell surface, to confer proliferatory activity in intact cells expressing the receptor.

Please substitute the paragraph beginning on page 26, line 25, with the following paragraph:

C39

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequence of the deposited cDNAs or the nucleic acid sequences shown in FIG. 1A-1B (SEQ ID NO:1), FIG. 4A-4C (SEQ ID NO:4),

or FIG. 7A-7C (SEQ ID NO:7) will encode polypeptides "having TR2 receptor activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having TR2 protein activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

C39 cont.

Please substitute the paragraph beginning on page 30, line 15, with the following paragraph:

The invention further provides isolated TR2 polypeptides having the amino acid sequence encoded by the deposited cDNAs, or the amino acid sequence in FIG. 1A-1B (SEQ ID NO:2), FIG. 4A-4C (SEQ ID NO:5), or FIG. 7A-7C (SEQ ID NO:8), or a peptide or polypeptide comprising a portion of the above polypeptides.

C40

Please substitute the paragraph beginning on page 31, line 21, with the following paragraph:

Thus, the fragment, derivative or analog of the polypeptides of FIG. 1A-1B (SEQ ID NO:2), FIG. 4A-4C (SEQ ID NO:5), and FIG. 7A-7C (SEQ ID NO:8), or that encoded by the deposited cDNAs, may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-

C41

life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

C41 Cont.

Please substitute the paragraph beginning on page 34, line 7, with the following paragraph:

The polypeptides of the present invention also include the polypeptide encoded by the deposited cDNAs including the leader; the polypeptide encoded by the deposited the cDNAs minus the leader (i.e., the mature protein); the polypeptides of FIG. 1A-1B (SEQ ID NO:2) or FIG. 4A-4C (SEQ ID NO:5) including the leader; the polypeptides of FIG. 1A-1B (SEQ ID NO:2) or FIG. 4A-4C (SEQ ID NO:5) including the leader but minus the N-terminal methionine; the polypeptides of FIG. 1A-1B (SEQ ID NO:2) or FIG. 4A-4C (SEQ ID NO:5) minus the leader; the polypeptide of FIG. 7A-7C (SEQ ID NO:8); the extracellular domain, the transmembrane domain, and the intracellular domain of the TR2 receptor shown in FIG. 1A-1B (SEQ ID NO:2); and polypeptides which are at least 80% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptides described above, and also include portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

C42

Please substitute the paragraph beginning on page 35, line 7, with the following paragraph:

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in FIG. 1A-1B (SEQ ID

C43

NO:2), FIG. 4A-4C (SEQ ID NO:5), or FIG. 7A-7C (SEQ ID NO:8) or to the amino acid sequence encoded by one of the deposited cDNA clones can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

C43 cont.

Please substitute the paragraph beginning on page 36, line 23, with the following paragraph:

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate TR2 receptor-specific antibodies include: a polypeptide comprising amino acid residues from about 39 to about 70 in FIG. 1 (amino acid residues 3 to 34 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 106 to about 120 in FIG. 1A-1B (amino acid residues 70 to 84 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 142 to about 189 in FIG. 1A-1B (amino acid residues 106 to 153 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 276 to about 283 in FIG. 1 (amino acid residues 240 to 247 in SEQ ID NO:2); a polypeptide comprising amino acid residues from about 39 to about 70 in FIG. 4A-4C (amino acid residues 3 to 34 in SEQ ID NO:5); a polypeptide comprising amino acid residues from about 99 to about 136 in FIG. 4A-4C (amino acid residues 63 to 100 in SEQ ID NO:5); a polypeptide comprising amino acid residues from about 171 to about 185 in FIG. 4A-4C (amino acid residues 135 to 149 in SEQ ID NO:5); a polypeptide comprising amino acid residues from about 56 to about

C44

C44 corrd. 68 in FIG. 7A-7C (SEQ ID NO:8); and a polypeptide comprising amino acid residues from about 93 to about 136 in FIG. 7A-7C (SEQ ID NO:8). As indicated above, the inventors have determined that the above polypeptide fragments are antigenic regions of the TR2 receptor proteins.

Please substitute the paragraph beginning on page 47, line 14, with the following paragraph:

C45 Antibodies according to the present invention may be prepared by any of a variety of methods using TR2 receptor immunogens of the present invention. Such TR2 receptor immunogens include the TR2 receptor protein shown in FIG. 1A-1B (SEQ ID NO:2) and the TR2-SV1 (FIG. 4A-4C (SEQ ID NO:5)) and TR2-SV2 (FIG. 7A-7C (SEQ ID NO:8)) polypeptides (any of which may or may not include a leader sequence) and polypeptide fragments of the receptors comprising the ligand binding, extracellular, transmembrane, the intracellular domains of the TR2 receptors, or any combination thereof.

In the Claims:

Please cancel claims 39-44, 51-56, 63-80, and 87-174 without prejudice or disclaimer of the subject matter thereof. Applicants reserve the right to pursue the subject matter of the canceled claims in continuing applications.

Please substitute the following claim 27 for the pending claim 27:

C46 27. (Once Amended) An isolated Human Tumor Necrosis Factor Receptor-Like 2 protein comprising amino acids 1 to 245 of SEQ ID NO:26.